95-161726/21 B02
BOOTS CO PLC
91.10.13 93GB-021162 (95.04.20) C07D 487/04, A61K 31/505 (C07D 239:00, 249:00, 487/04)
New end use of 1,2,4-triazolo[1,5-a]pyrimidine cpds. - for treatment and/or prevention of seizures, epilepsy and neurological damage e.g. stroke, brain trauma, head injury or haemorrhage (Eng)
C95-074901 N[AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW NL NO NZ PL PT RO RU SD SE SI SK TJ TT UA US UZ VN] RO[AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ]
Addnl. Data: HEAL D J, FERNANDEZ FERNANDEZ M I, SARGENT B
94.10.12 94WO-EP03364

1,2,4-triazolo[1,5-a]pyrimidine cpds. of formula (II) and their salts are new:

R_1 = H or 1-6C alkyl, 1-6C alkenyl or 1-6C alkanoyl opt. substd. by one or more of halo, CN, OH or NH_2;

R_2, R_3 = H or 1-6C alkyl, 1-6C alkenyl, 1-6C alkanoyl, 1-6C alkylthio, 1-6C alkylsulphinyl or 1-6C alkylsulphonyl opt. substd. by one or more of halo, CN, OH or NH_2;

B(6-D9, 14-J7, 14-N16) 3

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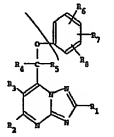

(II)

R_4, R_5 = H, 1-6C alkyl, opt. substd. by one or more of halo, CN, OH, NH_2 or 1-6C alkyl; or

CR_4R_5 = 3-6C cycloalkylidene opt. substd. by one or more of halo, CN, OH, NH_2 or 1-6C alkyl;

R_6, R_7, R_8 = H, halo, OH, SH, CN or 1-6C alkyl, 1-6C alkanoyl, 1-6C alkoxy, 2-6C alkoxycarbonyl, carboxy, 1-6C alkanoyloxy, 1-6C alkylthio, 1-6C alkylsulphinyl, 1-6C alkylsulphonyl, 1-6C alkylsulphonylamino, sulphamoyl, carbamoyl, 2-6C alkylcarbamoyl or 1-6C alkanoylamino opt. substd. by one or more of halo, CN, OH or amino and any N atom is opt. substd. by one or more 1-6C alkyl;

with the proviso that if R_1, R_2,R_3, R_4 and R_5 = H; R_3 = Me and either R_6, R_7 = H or R_6 = 4-chloro and R_7 is H or 2-chloro then cpd. (II) is not a racemate.

Also claimed is the use of cpds. (I), which are cpds. (II) excluding the proviso, as pharmaceuticals.

USE

Cpds. (I) and (II) can be used for the treatment, prophylaxis and/or inhibition of seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage, e.g. stroke, brain tumour, head injuries and haemorrhage. Cpds. (I) and (II) potentiate GABA-A transmission and/or activate neuronal K^+ channels.

Admin. may be oral, rectal, parenteral or topical. Typical unit dosage is 1-1,000 mg, prof. 5-500 mg.

SPECIFIC COMPOUNDS

21 cpds. (I) are claimed, e.g.:

7-[1-(4-fluorophenoxy)ethyl]-1,2,4-triazolo[1,5-a]pyrimidine (IIa);

7-[1-(4-methylsulphonylphenoxy)ethoxy]-1,2,4-triazolo [1,5-a]pyrimidine;

7-[1-(2-chloro-4-fluorophenoxy)ethyl]-1,2,4- triazolo[1,5-a]pyrimidine.

PREPARATION

Cpds. (II) are prepd. as follows (claimed):

(a)

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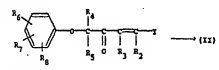
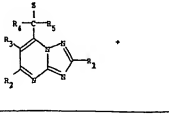
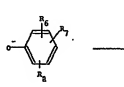


(XI)

Y = a leaving gp.

(b)



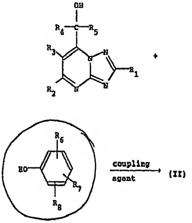


(XI)

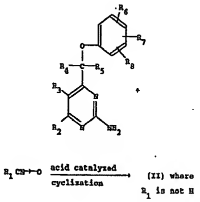
Z = a leaving gp.

(con't)

(c)



(d)



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EXAMPLE

1.12g of 4-fluorophenol was added to a stirred suspension of 0.48 g of NaH in 35 ml of dry 1,2-dimethoxyethane. The mixt. was stirred at room temp. for 30 mins., then a soln. of 2.27 g of 7-(1-bromoethyl)-1, 2, 4-triazolo[1, 5-a]pyrimidine in 85 ml of dry 1, 2-dimethoxyethane was added dropwise. The mixt. was stirred at room temp. for 24 hrs.. The NaBr was removed by filtration.

The solvent was evapd. and the residue dissolved in CH_2Cl_2 and washed with 200 ml of a 5% aq. soln. of NaOH, followed by water. The organic layer was dried ($MgSO_4$) and worked up to give 1.03 g of (IIa) m.pt. 106-108 °C. (AG)
(81pp2268DwgNo.0/0)
SR:WO8901478

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